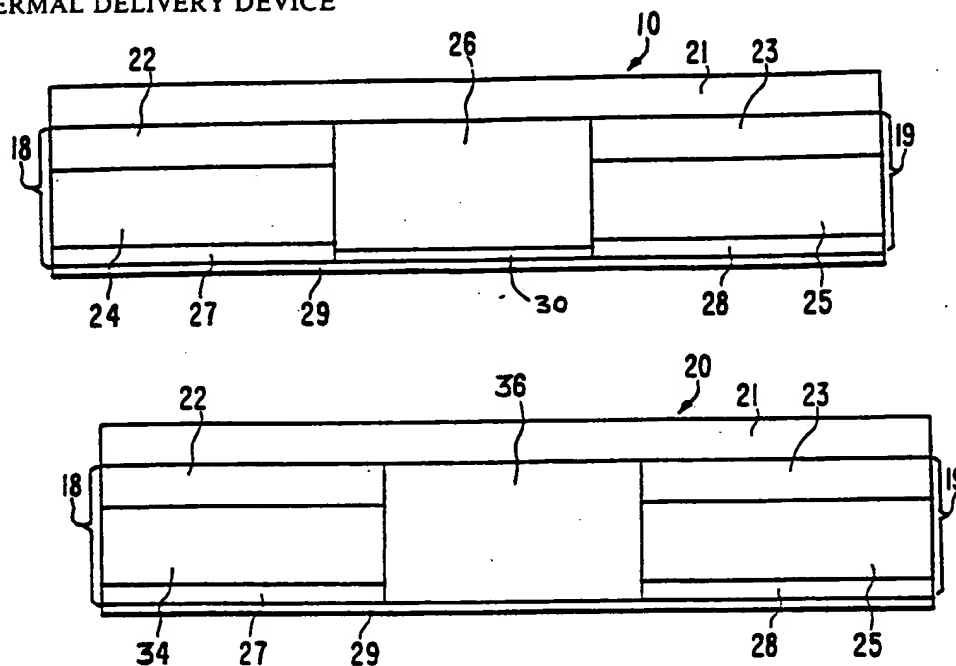




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(54) Title: TRANSDERMAL DELIVERY DEVICE



(57) Abstract

A transdermal drug delivery device (20) is provided having both an active drug reservoir (24) and a passive drug reservoir (26). Drug is actively delivered by iontophoresis from the active drug reservoir (24) by an electric field generated by a power source (21). Simultaneously, drug is delivered from passive reservoir (26) by passive (i.e., non-electrically assisted) diffusion. In one embodiment, the passive drug reservoir (26) is electrically insulated from the active drug reservoir (24). In a second embodiment, both the active and the passive drug are contained in the same reservoir (34). In the second embodiment, the active drug is ionizable while the passive drug is non-ionizable. Most preferably, the active drug is an ionizable form (i.e., a salt form) of the passive drug.

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TRANSDERMAL DELIVERY DEVICETECHNICAL FIELD

This invention relates to a device for delivering an agent transdermally or transmucosally. More particularly, this invention relates to such a delivery device which delivers an agent both passively (i.e., by diffusion) and actively using electrical power.

BACKGROUND ART

The transdermal route of parenteral delivery of drugs provides many advantages over other administrative routes. Passive transdermal systems which deliver a wide variety of agents by the physical process of diffusion are described in U.S. Patent Nos. 3,598,122; 3,598,123; 4,286,592; 4,314,557; 4,379,454 and 4,568,343, for example, all of which are incorporated herein by reference. A passive system in its simplest form consists of a polymeric reservoir having the agent to be delivered dispersed therethrough. The agent diffuses through the reservoir, across the reservoir-biological surface interface, and subsequently across the biological surface. When the biological surface is human skin, the stratum corneum layer of the skin is a complex barrier due to a chemical keratin-phospholipid complex which acts along with the horny layer as a barrier to the penetration of drugs into the body. The stratum corneum is known to both a lipophilic phase as well as a hydrophilic phase. In general, passive drug delivery involves the diffusion of drugs through the lipophilic phase of the stratum corneum and the underlying layers of the skin. As used herein, the term "passive" is defined as meaning drug delivery by diffusion and without electrical assistance. The term "biological surface" as used herein, is defined as including without limitation, skin, mucosal membranes, nails and blood vessel walls. In general, it is preferable to passively deliver non-ionized drugs and agents using a passive transdermal delivery system since ionized drugs and agents usually are unable to passively permeate through human skin at therapeutically effective rates.

A more recent method of transdermal drug delivery uses electrical current to actively transport agents across a biological surface. This concept is based upon basic principles of electrochemistry and is referred to herein as electrically assisted or iontophoretic delivery. Abramson and Gorin in J. Phys. Chem. 44, pp 1094-1102 (1940) showed that charged ions can be introduced into the skin under the influence of an electric field and that the pathways for transdermal ion transport are hydrophilic pathways in the skin. These hydrophilic pathways include the sweat glands and hair follicles. Thus, although both passive delivery devices and electrically-assisted delivery devices involve drug delivery through the skin, the transdermal pathways for drugs delivered from passive devices and electrically-assisted devices are quite different.

Iontophoresis, according to Dorland's Illustrated Medical Dictionary, is defined to be "the introduction, by means of electric current, of ions of soluble salts into the tissues of the body for therapeutic purposes."

Iontophoretic devices have been known since the early 1900's. British patent specification No. 410,009 (1934) described an iontophoretic device which overcame one of the disadvantages of such early devices known to the art at that time, namely the requirement of a special low tension (low voltage) source of current which meant that the patient needed to be immobilized near such source. The device of that British specification was made by forming a galvanic cell from the electrodes and the material containing the medicament or drug to be delivered transdermally. The galvanic cell produced the current necessary for iontophoretically delivering the medicament. This ambulatory device thus permitted iontophoretic drug delivery with substantially less interference with the patient's daily activities.

More recently, a number of United States patents have issued in the iontophoresis field, indicating a renewed interest in this mode of drug delivery. For example, Vernon et al U.S. Patent No. 3,991,755; Jacobsen et al U.S. Patent No. 4,141,359; Wilson U.S. Patent No. 4,398,545; and Jacobsen U.S. Patent No. 4,250,878 disclose examples of iontophoretic devices and some applications thereof. The iontophoresis process has been found to be useful in the transdermal

administration of medicaments or drugs including lidocaine hydrochloride, hydrocortisone, fluoride, penicillin, dexamethasone sodium phosphate, insulin and many other drugs. Perhaps the most common use of iontophoresis is in diagnosing cystic fibrosis by
5 delivering pilocarpine salts iontophoretically. The pilocarpine stimulates sweat production; the sweat is collected and analyzed for its chloride content to detect the presence of the disease.

In presently known iontophoretic devices, at least two electrodes are used. Both of these electrodes are disposed so as to
10 be in intimate electrical contact with some portion of the skin of the body. One electrode, called the active or donor electrode, is the electrode from which the ionic substance, medicament, drug precursor or drug is delivered into the body by electromigration (i.e., the movement of charged ions within an electric field imposed
15 across the body surface). The other electrode, called the counter, indifferent, inactive or return electrode, serves to close the electrical circuit through the body. In conjunction with the patient's skin contacted by the electrodes, the circuit is completed by connection of the electrodes to a source of electrical energy,
20 e.g., a battery. For example, if the ionic substance to be delivered into the body is positively charged (i.e., a cation), then the anode will be the active electrode and the cathode will serve to complete the circuit. If the ionic substance to be delivered is negatively charged (i.e., an anion), then the cathode will be the active
25 electrode and the anode will be the counter electrode.

Alternatively, both the anode and cathode may be used to deliver drugs of opposite charge into the body. In such a case, both electrodes are considered to be active or donor electrodes. For example, the anode can deliver a positively charged ionic substance
30 into the body while the cathode can deliver a negatively charged ionic substance into the body.

It is also known that iontophoretic delivery devices can be used to deliver an uncharged drug or agent into the body. This is accomplished by a process called electroosmosis. Electroosmosis is
35 the transdermal flux of a liquid solvent (e.g., the liquid solvent containing the uncharged drug or agent) which is induced by the presence of an electric field imposed across the skin by the donor

electrode. As used herein, the terms "iontophoresis" and "iontophoretic" refer to (1) the delivery of charged drugs or agents by electromigration, (2) the delivery of uncharged drugs or agents by the process of electroosmosis, (3) the delivery of charged drugs or agents by the combined processes of electromigration and electroosmosis, and/or (4) the delivery of a mixture of charged and uncharged drugs or agents by the combined processes of electromigration and electroosmosis.

As with passive transdermal delivery systems, iontophoretic delivery devices also require a reservoir or source of the beneficial agent to be delivered into the body. In general, it is preferable to deliver ionized drugs and agents using an iontophoretic delivery device. Examples of such reservoirs or sources of ionized or ionizable agents include a pouch as described in the previously mentioned Jacobsen U.S. Patent No. 4,250,878, or a pre-formed gel body as described in Webster U.S. Patent No. 4,383,529 and Ariura et al. U.S. Patent No. 4,474,570. Such drug reservoirs are electrically connected to the anode or the cathode of an iontophoresis device to provide a fixed or renewable source of one or more desired agents.

More recently, iontophoretic delivery devices have been developed in which the donor and counter electrode assemblies have a "multi-laminate" construction. In these devices, the donor and counter electrode assemblies are formed of multiple layers of (usually) polymeric matrices. For example, Parsi U.S. Patent 4,731,049 discloses a donor electrode assembly having hydrophilic polymer based electrolyte reservoir and drug reservoir layers, a skin-contacting hydrogel layer, and optionally one or more semipermeable membrane layers. Sibalís U.S. Patent No. 4,640,689 discloses in Figure 6 an iontophoretic delivery device having a donor electrode assembly comprised of a donor electrode (204), a first drug reservoir (202), a semipermeable membrane layer (200), a second drug reservoir (206), and a microporous skin-contacting membrane (22'). The electrode layer can be formed of a carbonized plastic, metal foil or other conductive films such as a metallized mylar film. In addition, Ariura et al, U.S. Patent 4,474,570 discloses a device wherein the electrode assemblies include a conductive resin film electrode layer, a hydrophilic gel reservoir layer, a current

distribution and conducting layer and an insulating backing layer. Ariura et al disclose several different types of electrode layers including an aluminum foil electrode, a carbon fiber non-woven fabric electrode and a carbon-containing rubber film electrode.

5 Transdermal iontophoretic delivery devices having electrodes composed of electrochemically inert materials, as well as devices having electrodes composed of electrochemically reactive materials are known. Examples of electrochemically inert electrode materials include platinum, carbon, gold and stainless steel. The prior art
10 has also recognized that the electrochemically reactive electrode materials are in many cases preferred from the standpoint of drug delivery efficiency and pH stability. For example, U.S. Patent Nos. 4,744,787; 4,747,819 and 4,752,285 all disclose iontophoretic electrodes composed of materials which are either oxidized or reduced
15 during operation of the device. Particularly preferred electrode materials include silver as the anodic electrode, and silver chloride as the cathodic electrode.

A primary advantage of passive transdermal delivery systems over electrically assisted iontophoretic delivery devices is cost.
20 Because passive systems do not require any source of electrical power and the attendant electrical circuitry, the cost of a passive system is significantly less than an electrically powered iontophoretic delivery device adapted to deliver the same drug. Passive systems are also typically much easier to manufacture in part because of
25 their simpler construction and lack of any electrical components. On the other hand, passive systems can only be used to deliver those drugs which are able to permeate through skin at pharmacologically effective rates. Because human skin presents a significant barrier to passive drug permeation, relatively few drugs have been found to
30 be suitable for passive delivery systems.

Electrically assisted iontophoretic delivery devices on the other hand have the ability to deliver many drugs at therapeutically effective rates, including drugs having high molecular weights such as polypeptides and proteins, which cannot be delivered at
35 therapeutically effective rates by passive transdermal delivery systems. In addition, electrically assisted iontophoretic delivery devices provide other advantages over passive transdermal delivery

systems. One advantage is the shorter time required to reach pharmacologically effective transdermal drug delivery rates. Electrically assisted devices can achieve pharmacologically effective transdermal delivery rates within several minutes of start-up whereas
5 passive transdermal delivery systems typically require much longer start-up periods. A second advantage of electrically assisted iontophoretic delivery devices is the degree of control over the amount and rate of drug delivered from the device, which can be achieved simply by controlling the level of electrical current
10 applied by the device. A third advantage of electrically-assisted iontophoretic delivery devices is their ability to be programmed to deliver drug at a predetermined regimen and their ability to deliver either a bolus dose or to deliver medication "on demand" in applications such as the delivery of narcotic analgesics for
15 treatment of pain. Passive transdermal delivery systems do not have these active control features and simply deliver drug at a rate predetermined by the design of and the materials used in, the passive system.

It is therefore an object of this invention to provide a
20 transdermal delivery device having the advantages of a passive transdermal delivery system and the advantages of an electrically assisted iontophoretic delivery device.

In particular, it is an object of the present invention to provide a transdermal delivery device, at least a portion of which is
25 electrically powered and capable of delivering an agent transdermally by iontophoresis, and therefore able to deliver drugs transdermally at therapeutically effective rates with a minimal start-up time and in preprogrammed or on demand delivery regimens.

It is a further object of the present invention to provide a
30 transdermal agent delivery device, at least a portion of which delivers drugs transdermally by passive non-electrically assisted delivery and which is able to deliver agent without consuming electrical power.

DISCLOSURE OF THE INVENTION

These and other important objects of the present invention are met by a transdermal agent delivery device including an active agent reservoir which is adapted to be placed in active agent transmitting relation with a body surface. The active agent reservoir is positioned within an electric field generated by a source of electrical power which is electrically connected to the active agent reservoir. The delivery device also includes a passive agent reservoir adapted to be placed in passive agent transmitting relation to a body surface. The passive agent contained in the passive agent reservoir is able to passively diffuse through the passive agent reservoir and through the body surface. In one embodiment of the invention, the passive agent reservoir is electrically insulated from the electrical field generated by the power source. When placed on a body surface, the device delivers active agent by iontophoresis and passive agent by diffusion.

In another embodiment of the invention, the active agent and the passive agent are present in the same reservoir, which combined active agent and passive agent reservoir is positioned within an electric field generated by a source of electrical power which is electrically connected to the agent reservoir. In this embodiment, the active agent is in the form of charged ions which are delivered by the electric field by the process of electromigration. The passive agent is non-ionized and is delivered primarily by passive diffusion.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic view of a transdermal drug delivery device according to the present invention; and

Figure 2 is a schematic view of another embodiment of a transdermal drug delivery device according to the present invention.

MODES FOR CARRYING OUT THE INVENTION

Figure 1 is a schematic view of a delivery device 10 for delivering a beneficial agent through a body surface such as intact skin or a mucosal membrane. Delivery device 10 includes an iontophoretic donor electrode assembly 18 and an iontophoretic counter electrode assembly 19. Electrode assemblies 18 and 19 are connected in series by top layer 21 which contains an electrical power source, typically one or more low voltage batteries, and an optional control circuit (e.g., a resistor, a transistor-based current control circuit, an on-off switch and/or a microprocessor) adapted to control the current output of the power source over time. When the device 10 is in storage, no current flows because the device does not form a closed circuit. When the device 10 is placed on the skin or mucosal membrane of a patient and the electrode assemblies 18 and 19 are hydrated, the circuit between the electrodes is closed and the power source begins to deliver current through the device and through the body of the patient. The donor and counter electrode assemblies 18 and 19 are adhered to the skin by means of ion-conducting adhesive layers 27 and 28. The device also includes a strippable release liner 29 which is removed just prior to application to the body. As an alternative to the ion-conducting adhesive layers 27 and 28 shown in Figure 1, the iontophoretic delivery device 10 may be adhered to the skin using an adhesive overlay. Any of the conventional adhesive overlays used to secure passive transdermal delivery devices to the skin may be used.

The donor electrode assembly 18 includes a donor electrode 22 and an active agent reservoir 24. The active agent reservoir 24 contains the beneficial agent to be iontophoretically delivered by device 10. The counter electrode assembly 19 includes a counter electrode 23 and an electrolyte reservoir 25. The electrolyte reservoir 25 contains a suitable pharmacologically acceptable salt. Suitable salts include sodium chloride, alkali metal salts, alkaline earth metal salts such as chlorides, sulfates, nitrates, carbonates, phosphates, and organic salts such as ascorbates, citrates, acetates and mixtures thereof. Reservoir 25 may also contain a buffering agent. Sodium chloride is a suitable electrolyte when the counter

electrode 23 is the cathode and is composed of silver/silver chloride, optionally with a sodium phosphate buffer. The donor and counter electrode assemblies 18 and 19 are physically attached to, and separated by, a reservoir 26 and form a single self-contained unit therewith.

Reservoir 26 performs two functions. In connection with the iontophoretic electrode assemblies 18 and 19 of device 10, reservoir 26 acts as an insulator between electrodes assemblies 18 and 19. Because reservoir 26 is in intimate contact with both the active agent reservoir 24 and the electrolyte reservoir 25, the reservoir 26 must be substantially impermeable to the free passage of ionic species. In this way, reservoir 26 prevents the electrode assemblies 18 and 19 from short circuiting by preventing direct electrical and/or ion transport between the electrode assemblies 18 and 19. Accordingly, reservoir 26 is formed of a material which is substantially impermeable to the passage of ions. Reservoir 26 is preferably formed of a hydrophobic non-conducting polymeric material which is impermeable to both the passage of ions and water. Most preferably the matrix of reservoir 26 is formed of an ethylene vinyl acetate copolymer.

In addition, reservoir 26 also functions as the reservoir for the passive agent. This function will be described in more detail hereinafter.

Electrodes 22 and 23 are electrically conductive and may be formed of a metal, e.g., a metal foil or metal deposited or painted on a suitable backing. Examples of suitable metals include silver, zinc, silver/silver chloride, aluminum, platinum, stainless steel, gold and titanium. Alternatively, the electrodes 22 and 23 may be formed of a hydrophobic polymer matrix containing a conductive filler such as a metal powder, powdered graphite, carbon fibers or other known electrically conductive filler material. The hydrophobic polymer based electrodes may be made by mixing the conductive filler in the hydrophobic polymer matrix. For example, zinc powder, silver powder, silver/silver chloride powder, powdered carbon, carbon fibers and mixtures thereof can be mixed in a hydrophobic polymer (e.g., a polyisobutylene rubber) matrix, with the preferred amount of

conductive filler being within the range of about 30 to 90 vol% and the remainder being the hydrophobic polymer matrix.

Electrodes 22 and 23 are electrically connected to the power source in layer 21 using well known means, e.g., printed flexible circuits, metal foils, wires, electrically conductive adhesives or by direct contact. As an alternative to a battery as the power source, device 20 can be powered by a galvanic couple formed by the donor electrode 22 and counter electrode 23 being composed of dissimilar electrochemical couples and being placed in electrical contact with one another. Typical galvanic couple materials for delivering a cationic agent include a zinc donor electrode 22 and a silver/silver chloride counter electrode 23. A Zn-Ag/AgCl galvanic couple provides an electrical potential of about 1 volt.

Regardless of the source of electrical power used, the power source in combination with the electrode assemblies 18 and 19 and the patient's body completes the circuit and generates an electrical field across the body surface (eg, skin) to which device 10 is applied. This electrical field runs from the power source in layer 21, through the electrode 22, through the active agent reservoir 24, through the adhesive layer 27, through the body of the patient, through the adhesive layer 28, through the electrolyte reservoir 25, through the electrode 23 and back to the power source in layer 21. The electric field generated by the power source causes active agent ions within reservoir 24 to be delivered through adhesive layer 27 and into the body by the process of electromigration.

In the embodiment shown in Figure 1, the passive reservoir 26 is electrically insulated from the electric field generated by the power source in layer 21. Passive reservoir 26 may be insulated from the electric field by any number of conventional means. The most preferred way of isolating the passive agent from the electric field is to choose an electrically insulating material as the matrix for passive reservoir 26. Most preferably, the matrix of reservoir 26 is comprised of a hydrophobic polymer such as polyisobutylene or ethylene vinyl acetate. These hydrophobic polymers do not hold water, water being the preferred solvent for solubilizing drug salts delivered iontophoretically, and therefore hydrophobic polymers do

not allow transport of ions therethrough and thereby act as electrical insulators.

Alternatively, the passive reservoir 26 may be composed of a conductive matrix, such as a hydrophilic polymer, which has an insulating layer separating the passive agent reservoir 26 from the active agent reservoir 24, the electrolyte reservoir 25, the electrodes 22 and 23 and the ion-conducting adhesive layers 27 and 28 (if present). The insulating layer can be a layer of a hydrophobic polymer (eg, polyethylene) or simply a space which separates the passive reservoir 26 from the current conducting portions of the device and thereby prevents current from passing directly from electrodes 22 and reservoir 24, through passive reservoir 26, to electrode 23 and reservoir 25. In either case, no electrical current passes through passive reservoir 26 and the passive agent within reservoir 26 is not subject to any electric field effects when the device 10 applies current through the body.

Reservoir 26 contains a passive agent adapted to be delivered into the body surface without electrical assistance. The passive agent reservoir 26, in addition to being insulated from the electric field generated by the power source, must also be permeable to the passive (i.e., non-electrically assisted) diffusion of the passive agent therethrough. Thus, the passive agent reservoir matrix is made from a material in which the passive agent is soluble and/or the passive agent reservoir matrix is microporous and has a structure that enables the passive agent to pass through the pre-existing pores or capillaries, either by diffusive permeability or microporous hydrodynamic flow.

Because the delivery of passive agent is not affected by the electric field generated by the power source, the passive agent delivery rate will be substantially independent of the amount of current applied by the device and will not be affected by the activation or the deactivation of the electrically assisted portions of the device. In this manner, the passive agent reservoir may be used to provide a baseline delivery of drug or other beneficial agent to the patient. The baseline delivery rate may then be supplemented by activating the electrically assisted portions of the device.

In order to control the passive agent delivery rate, it is possible to adjust the concentration of passive agent in the reservoir matrix. Alternatively, the composition or form of the matrix material can be chosen in accordance with well known principles. For example, if a constant passive drug delivery rate is required, it is generally preferable to provide an amount of passive agent in excess of saturation concentration in the passive reservoir matrix. In many cases, the skin itself provides a suitable limit on the maximum rate at which drug is passively delivered from reservoir 26 into the body. In those cases where a lower passive delivery rate is desired, an optional flux control membrane 30 (e.g., a microporous membrane) may be provided on the skin side of the passive agent reservoir 26 which exhibits a passive agent flux which is less than the flux through the body surface to which the device 10 is applied.

As is known in the art, the selection of appropriate materials for controlling the passive agent flux through either the membrane 30 or the passive agent reservoir matrix material will be dependent on the particular passive agent to be delivered from reservoir 26. Both organic and inorganic polymeric materials can be shaped into a wide variety of forms with tailored morphology and a wide range of chemical and physical properties to advantageously control release of a wide variety of agents, including those with large molecular structures such as peptides and proteins, and over a large dosage rate range. In the case of microporous matrix or membrane materials, by impregnating the interconnected pores of the microporous structure with a diffusive medium for the passive agent to be administered, a given microporous membrane or matrix material can be adapted to control the release of agents having a wide range of chemical properties by diffusive permeability. Thus, by varying the concentration of passive agent in the reservoir 26, as well as the composition, pore size, and effective thickness of the rate controlling matrix or membrane material, the viscosity of the drug to be administered by appropriate formulation or by impregnating the material with suitable solvent, the dosage rate per area of passive agent reservoir 26 can be controlled since the material functions to meter the flow of drug from the device. Therefore, passive agent reservoirs having the same surface area can provide different dosages

of a passive agent by varying the above discussed parameters in accordance with well known principles.

Suitable matrices for the passive agent reservoir 26 and/or the membrane 30 include, without limitation, natural and synthetic rubbers such as polybutylene, polyisobutylene, polybutadiene, polyethylene, styrenebutadiene, copolymers, polyisoprene, polyurethane, ethylene/propylene copolymers, polyalkylacrylate polymers, copolyesters, ethylene/acrylic copolymers, silicones and butadiene/acrylonitrile copolymers for example and other polymers such as the ethylene vinylacetate (EVA) polymers described in U.S. Patent No. 4,144,317, which is incorporated herein by reference. Typically the drug is dispersed through the matrix or carrier at a concentration in excess of saturation, the amount of the excess being a function of the intended useful life of the system. The drug, however, may be present at initial levels below saturation without departing from this invention.

In addition to the drug, the passive agent reservoir 26 may also contain other materials such as permeation enhancers, dyes, pigments, inert fillers, excipients, and conventional components of pharmaceutical products or transdermal therapeutic systems as known to the art.

The passive reservoir 26, or membrane 30 if one is used, should be in firm contact with the patient's skin or mucosa when device 10 is placed on the body. Flow of drug from the passive agent reservoir 26 is metered through the reservoir matrix material in accordance with the laws of hydrodynamics or diffusion, as herein discussed, at a predetermined rate. In operation, drug molecules are continuously removed from the reservoir and diffuse to the skin or mucosa of the patient. In the case of systemic drugs, the drugs are transported through the skin or mucosa and enter circulation through the capillary network.

Turning now to the active (i.e., electrically assisted) portions of the device, the active agent reservoir 24 and the electrolyte reservoir 25 are each comprised of a hydrophilic polymer, most preferably a mixture of a hydrophilic polymer and a hydrophobic polymer, and most preferably a mixture of about 10 to 60 wt% of a hydrophilic polymer and about 10 to 60 wt% of a hydrophobic polymer

on a dry weight basis. The agent reservoir matrix typically contains about 1 to 60 wt% of the agent. The electrolyte reservoir matrix typically contains about 0.5 to 60 wt% of the electrolyte.

As used herein, a hydrophilic polymer is a polymer having an equilibrium water content of at least 20 wt%, preferably at least about 30 wt% and most preferably at least about 40 wt% after prolonged exposure to an atmosphere having a relative humidity of over about 90%. Also as used herein, a hydrophobic polymer is any polymer having an equilibrium water content of less than 20 wt%, preferably less than about 15 wt% and most preferably less than about 10 wt% after prolonged exposure to an atmosphere having a relative humidity of over about 90%.

Preferably, the hydrophobic polymer is heat fusible and can be heat fused to another polymeric surface such as a polymer based electrode or a membrane. Alternatively, if the electrode is composed of a metal, such as a metal plate, a metal foil or a metallized surface on a suitable backing material, the hydrophobic polymer may require a resinous tackifying agent.

Suitable hydrophobic polymers for use in the matrix of reservoirs 24 and 25 include, without limitation, polyethylene, polypropylene, polyisoprenes and polyalkenes, rubbers, copolymers such as Kraton®, polyvinylacetate, ethylene vinyl acetate copolymers, polyamides such as nylons, polyurethanes, polyvinylchloride, acrylic or methacrylic resins such as polymers of esters of acrylic or methacrylic acid with alcohols such as n-butanol, n-pentanol, isopentanol, 2-methyl butanol, 1-methyl butanol, 1-methyl pentanol, 2-methyl pentanol, 3-methyl pentanol, 2-ethyl butanol, isooctanol, n-decanol, or n-dodecanol, alone or copolymerized with ethylenically unsaturated monomers such as acrylic acid, methacrylic acid, acrylamide, methacrylamide, N-alkoxymethyl acrylamides, N-alkoxymethyl methacrylamides, N-tert-butylacrylamide, and itaconic acid, N-branched alkyl maleamic acids wherein the alkyl group has 10-24 carbon atoms, glycol diacrylates, and blends thereof. Most of the above listed hydrophobic polymers are heat fusible. Of these, polyisobutylene rubbers and ethylene vinyl acetate copolymers are preferred.

In cases where the electrode is a metal foil or a metallized polymeric film, it may be necessary to add a tackifying resin to the hydrophobic polymer component in order to enhance its adhesiveness. Suitable hydrophobic polymers which can be rendered more adhesive by the addition of tackifying resins include, without limitation, cellulose acetate, cellulose acetate butyrate, ethylcellulose, polyurethanes, poly(styrene-butadiene) and poly(styrene-isoprene-styrene) block copolymers, ethylene vinyl acetate copolymers such as those which are described in U.S. Patent No. 4,144,317, plasticized or unplasticized polyvinylchloride, natural or synthetic rubbers, C₂-C₄ polyolefins such as polyethylene, polyisoprene, polyisobutylene and polybutadiene. Examples of suitable tackifying resins include, without limitation, fully hydrogenated aromatic hydrocarbon resins, hydrogenated esters and low molecular weight grades of polyisobutylene. Particularly suitable are tackifiers sold by Hercules, Inc. of Wilmington, DE under the trademarks Staybelite Ester® #5 and #10, Regal-Rez® and Piccotac®.

Suitable hydrophilic polymers for use in the matrix of reservoirs 24 and 25 include polyvinylpyrrolidones, polyvinyl alcohol, polyethylene oxides such as Polyox® manufactured by Union Carbide Corp., Carbopol® manufactured by BF Goodrich of Akron, OH; blends of polyoxyethylene or polyethylene glycols with polyacrylic acid such as Polyox® blended with Carbopol®, polyacrylamide, Klucel®, cross-linked dextran such as Sephadex (Pharmacia Fine Chemicals, AB, Uppsala, Sweden), Water Lock® (Grain Processing Corp., Muscatine, Iowa) which is a starch-graft-poly(sodium acrylate-co-acrylamide) polymer, cellulose derivatives such as hydroxyethyl cellulose, hydroxypropylmethylcellulose, low-substituted hydroxypropylcellulose, and cross-linked Na-carboxymethylcellulose such as Ac-Di-Sol (FMC Corp., Philadelphia, Pa.), hydrogels such as polyhydroxyethyl methacrylate (National Patent Development Corp.), natural gums, chitosan, pectin, starch, guar gum, locust bean gum, and the like, along with blends thereof. Of these, polyvinylpyrrolidones are preferred.

Blending of the drug or electrolyte with the polymer matrix is done mechanically, either in solution or by milling, extrusion or hot melt mixing, for example. The resulting reservoir layers may then be

prepared by solvent casting, extrusion or by melt processing, for example.

In addition to the drug and electrolyte, the reservoirs 24 and 25 may also contain other conventional materials such as dyes, pigments, inert fillers, and other excipients.

Layer 21 preferably contains electrical circuitry for controlling the level of current produced by device 10. The control circuit may take the form of an on-off switch for "on-demand" drug delivery (e.g., patient controlled delivery of an analgesic for pain relief), a timer, a fixed or variable electrical resistor, a controller which automatically turns the device on and off at some desired periodicity to match the natural or circadian patterns of the body, or other more sophisticated electronic control devices known in the art. For example, it may be desirable to deliver a predetermined constant level of current from device 10 since a constant current level ensures that the active agent is delivered through the skin at a constant rate. The current level can be controlled by a variety of known means, for example, a resistor or a simple circuit that employs a resistor and a field effect transistor. Control circuit may also include an integrated circuit which could be designed to control the dosage of active agent, or even to respond to sensor signals in order to regulate the dosage to maintain a predetermined dosage regimen. A relatively simple circuit can control the current as a function of time, and if desired, generate complex current waveforms such as pulses or sinusoidal waves. In addition, the control circuit 19 may employ a bio-feedback system which monitors a bio-signal, provides an assessment of the therapy, and adjusts the active agent delivery accordingly. A typical example is the monitoring of the blood sugar level for controlled administration of insulin to a diabetic patient.

As an alternative to the side-by-side alignment of the donor electrode assembly 18, the passive agent reservoir 26 and the counter electrode assembly 19 shown in Figures 1 and 2, the electrode assemblies can be concentrically aligned with the counter electrode assembly 19 positioned centrally and surrounded by an angularly shaped passive agent reservoir 26 which is in turn surrounded by an angularly shaped donor electrode assembly 18. The electrode assemblies can, if desired, be reversed with the counter electrode

assembly surrounding the centrally positioned donor electrode assembly. The concentric alignment of the electrode assemblies can be circular, elliptical, rectangular or any of a variety of geometric configurations.

5 The combined skin-contacting areas of electrode assemblies 18 and 19 can vary from less than 1 cm² to greater than 200 cm². The average device however, will have electrode assemblies with a combined skin-contacting area within the range of about 5-50 cm². The skin-contacting area of passive agent reservoir 26 or membrane 30
10 can vary from about 1 to 100 cm², and most typically from about 5 to 25 cm².

A second embodiment of the invention is shown in Figure 2. Like the device illustrated in Figure 1, device 20 also includes a donor electrode assembly 18 and a counter electrode assembly 19. The
15 donor electrode assembly 18 and the counter electrode assembly 19 may be adhered to the body surface using ion-conducting adhesive layers 27 and 28, respectively. Device 20 also includes a donor electrode 22 and a counter electrode 23 which are electrically connected to layer 21 containing electrical circuitry and a power source.

20 Unlike device 10 illustrated in Figure 1 however, device 20 utilizes an electrically insulating separator 36 which contains no passive agent. In device 20, both the active agent and the passive agent are contained within agent reservoir 34. In this embodiment of the invention, the active agent is in the form of charged ions which
25 are actively delivered by the electric field generated by the power source in layer 21. The passive agent contained in reservoir 34 is non-ionizable (i.e., the passive agent is in the form of uncharged molecules) and is passively delivered through the body surface due to the concentration gradient between the high concentration of the
30 passive agent in reservoir 24 and the low concentration of the passive agent within the body. The passive agent concentration gradient causes the passive agent to be passively delivered from reservoir 34 both when the power source in layer 21 is activated (and thus when the electric field is generated) and when the power source
35 in layer 21 is turned off. Of course when the power source is turned on and the electric field through reservoir 34 is generated, some relatively small amount of the passive agent is actively delivered by

the phenomenon of electroosmosis. However, the electroosmosis flux component will typically be much smaller (eg, less than 20%) than the passive flux component of the passive agent. Of course in cases where the active agent and the passive agent are merely different forms of the same chemical entity (eg, the passive agent is a narcotic analgesic in the form of a base and the active agent is an ionizable salt of the base), then the relative size of the electroosmotic component becomes inconsequential since the electroosmotic flux component of the passive agent can be considered merely a portion of the total electrically assisted flux. However, in cases where the active agent and the passive agent are not chemically related (eg, the passive agent is an anti-inflammatory in acid form, such as ibuprofen, and the active agent is an antibiotic in salt form, such as tetracycline HCl), it is desirable to minimize the electroosmotic flux of the passive agent so that delivery of the passive agent remains substantially independent of whether or not the power source is activated. By minimizing the electroosmotic flux of the passive agent to less than 20%, and preferably less than 10%, of the passive flux of the passive agent, the delivery of passive agent from device 20 is substantially unaffected by the amount of current passing through reservoir 34. Thus, the delivery of passive agent is substantially unaffected by the activation or deactivation of the electrical portions of the device. Also like the device in Figure 1, the passive delivery of the passive agent may provide a baseline delivery of drug or beneficial agent which can be supplemented by activating the electrically assisted portions of the device and actively delivering the active agent.

In the second embodiment of the invention, the matrix of reservoir 34 preferably comprises a mixture of a hydrophilic polymer and a hydrophobic polymer. Most preferably, the active agent in reservoir 34 is a water soluble drug salt and therefore is delivered along the hydrated hydrophilic polymer pathways through reservoir 34. Likewise, the passive agent in reservoir 34 most preferably diffuses along the non-hydrated, hydrophobic polymer pathways through reservoir 34.

This invention has utility in connection with the delivery of drugs within the class which can be delivered through body surfaces.

Of course, it will be understood from the description herein that the term "passive agent" is limited to those therapeutically active substances which are preferably in the form of neutral, uncharged molecules and which are able to passively diffuse through a matrix and/or membrane and through a body surface at a therapeutically effective rate. Similarly, the term "active agent" is limited to therapeutically active substances which are preferably in the form of charged ions and which are able to be delivered through a body surface by iontophoresis at therapeutically effective rates. As used herein, the expressions "agent" and "drug" are used interchangeably and are intended to have their broadest interpretation as any therapeutically active substance which is delivered to a living organism to produce a desired, usually beneficial, effect. In general, this includes therapeutic agents in all of the major therapeutic areas including, but not limited to, anti-infectives such as antibiotics and antiviral agents, analgesics including fentanyl, sufentanil, buprenorphine and analgesic combinations, anesthetics, anorexics, antiarthritics, antiasthmatic agents such as terbutaline, anticonvulsants, antidepressants, antidiabetic agents, antidiarrheals, antihistamines, anti-inflammatory agents, antimigraine preparations, antiontossickness preparations such as scopolamine and ondansetron, antinauseants, antineoplastics, antiparkinsonism drugs, cardiostimulants such as dobutamine, antipruritics, antipsychotics, antipyretics, antispasmodics, including gastrointestinal and urinary, anticholinergics, sympathomimetics, xanthine derivatives, cardiovascular preparations including calcium channel blockers such as nifedipine, beta-blockers, beta-agonists such as salbutamol and ritodrine, antiarrhythmics, antihypertensives such as atenolol, ACE inhibitors such as enalapril, diuretics, vasodilators, including general, coronary, peripheral and cerebral, central nervous system stimulants, cough and cold preparations, decongestants, diagnostics, hormones such as parathyroid hormone, hypnotics, immunosuppressives, muscle relaxants, parasympatholytics, parasympathomimetics, prostaglandins, proteins, peptides, psychostimulants, sedatives and tranquilizers.

The invention is also useful in the active delivery of peptides, polypeptides, proteins and other macromolecules. These

macromolecular substances typically have a molecular weight of at least about 300 daltons, and more typically a molecular weight in the range of about 300 to 40,000 daltons. Specific examples of peptides and proteins in this size range include, without limitation, LHRH, LHRH analogs such as buserelin, gonadorelin, nafarelin and leuprolide, GHRH, GHRF, insulin, insulotropin, heparin, calcitonin, octreotide, endorphin, TRH, NT-36 (chemical name: N=[[(s)-4-oxo-2-azetidiny]carbonyl]-L-histidyl-L-prolinamide), liprecin, pituitary hormones (e.g., HGH, HMG, HCG, desmopressin acetate, etc.), follicle luteoids, α ANF, growth factors such as growth factor releasing factor (GFRF), β MSH, somatostatin, bradykinin, somatotropin, platelet-derived growth factor, asparaginase, bleomycin sulfate, chymopapain, cholecystokinin, chorionic gonadotropin, corticotropin (ACTH), erythropoietin, epoprostenol (platelet aggregation inhibitor), glucagon, hirulog, hyaluronidase, interferon, interleukin-1, interleukin-2, menotropins (urofollitropin (FSH) and LH), oxytocin, streptokinase, tissue plasminogen activator, urokinase, vasopressin, desmopressin, ACTH analogs, ANP, ANP clearance inhibitors, angiotensin II antagonists, antidiuretic hormone agonists, antidiuretic hormone antagonists, bradykinin antagonists, CD4, ceredase, CSF's, enkephalins, FAB fragments, IgE peptide suppressors, IGF-1, neurotrophic factors, colony stimulating factors, parathyroid hormone and agonists, parathyroid hormone antagonists, prostaglandin antagonists, pentigetide, protein C, protein S, renin inhibitors, thymosin alpha-1, thrombolytics, TNF, vaccines, vasopressin antagonist analogs, alpha-1 anti-trypsin (recombinant), and TGF-beta.

Having thus generally described the invention, the following examples will illustrate preferred embodiments thereof.

EXAMPLE I

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A therapeutic system designed to transdermally deliver fentanyl, a narcotic analgesic, has a configuration similar to that illustrated in Figure 1 and is made of the following materials. The anodic donor electrode 22 is composed of a polymer matrix containing silver particles. The electrode is made by mixing powdered silver and cross-linked polyvinylpyrrolidone into a polyisobutylene matrix.

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The anodic donor electrode is comprised of 27.5 g polyisobutylene (PIB) having a molecular weight of 1,200,000 (sold by Exxon Corp. of Irving, TX), 27.5 g of PIB having a molecular weight of 35,000 (sold by Exxon Corp.), 20 g of polyvinylpyrrolidone (PVP-XL 10 sold by GAF Corp. of Wayne, NJ) and having a degree of cross-linking of 10%, and 25 g of silver powder having an average particle size of about 8 microns. The active agent reservoir 24 is composed of 32.5 wt% PIB (molecular weight of 1,200,000), 32.5 wt% PIB (molecular weight of 35,000), 25 wt% PVP-XL 10 and 10 wt% fentanyl HCl. Fentanyl HCl is water soluble. Thus, when the active agent reservoir 24 is hydrated, the fentanyl salt dissolves to form fentanyl drug ions (cations) and chloride counter ions (anions).

The ion-conducting adhesive layers 27 and 28 are composed of 16 wt% PIB (molecular weight of 1,200,000), 64 wt% PIB (molecular weight of 35,000), and 20 wt% PVP-XL 10. The counter electrode assembly 19 has substantially the same composition as the donor electrode assembly except the cathodic counter electrode 23 contains 25 wt% AgCl in place of the silver and the electrolyte reservoir 25 contains 10 wt% NaCl in place of fentanyl HCl. The skin contacting area of each of the electrode assemblies 18 and 19 is 10 cm².

The electronic layer 21 contains three 3-volt lithium button-cell batteries arranged in series and electrically connected between the donor electrode 22 and the counter electrode 23. An on-off switch is provided as a means for activating the electrically assisted (i.e., active delivery) portions of the device. When activated, the power source, in combination with a current controller, provides a current of 0.6 mA (i.e., a current density of 60 $\mu\text{A}/\text{cm}^2$) which is sufficient to deliver about 25 μg of fentanyl over a period of 5 minutes.

The passive (i.e., non-electrically assisted) delivery portion of the device is comprised of the passive drug reservoir 26 and a rate controlling membrane 30. The passive drug reservoir 26 has an aqueous gel core with a backing layer comprised of a multilaminate of polyethylene, aluminum, polyester and ethylene vinyl acetate copolymer. The exterior surface of the backing layer is in contact with electrode assembly 18, electrode assembly 19 and the bottom

surface of layer 21. The multilaminate backing layer provides an insulating layer between electrode assemblies 18 and 19.

The aqueous gel core of passive drug reservoir 26 is composed of 1 wt% fentanyl base, 2 wt% hydroxyethylcellulose and 97 wt% of a 25% solution of ethanol in water. Fentanyl base is in the form of neutral, uncharged molecules. The flux control membrane 30 is composed of an ethylene vinyl acetate copolymer having a vinyl acetate content of 9%. A layer of silicone adhesive, having a thickness of 2 mils, is applied to the skin side of the flux control membrane 30. The passive drug reservoir 26 has a skin contacting area of 10 cm, and releases fentanyl base at the rate of 25 $\mu\text{g/hr}$.

The fentanyl delivery system provides a base line fentanyl base delivery rate of 25 $\mu\text{g/hr}$ from the passive drug reservoir 26. The electrically assisted portions of the device enable the system to deliver a bolus of 25 μg of ionic fentanyl every 5 minutes while the electrically assisted portion is in operation. Thus, when the electrically assisted portions are activated, the total fentanyl delivery rate from the system is about 325 $\mu\text{g/hr}$.

EXAMPLE II

A therapeutic system designed to transdermally deliver both fentanyl by passive delivery and metoclopramide by active delivery has a configuration similar to that illustrated in Figure 12 and is made of the same materials used in the device of Example I with the following exceptions. First, the active drug reservoir 24 is composed of 20 wt% PIB (molecular weight of 1,200,000), 20 wt% PIB (molecular weight of 35,000), 35 wt% of metoclopramide HCl and 25 wt% PVP-XL 10. Metoclopramide HCl is water soluble. Thus, when the active drug reservoir 24 is hydrated the metoclopramide salt dissolves and forms metoclopramide drug ions (cations) and chloride counter ions (anions). The donor electrode assembly 18 and the counter electrode assembly 19 each have a skin contacting area of 15 cm^2 . The current applied by the electrically assisted portions of the device is 1.5 mA.

The device delivers fentanyl base passively from the passive drug reservoir 26, similar to the device described in Example I. The

passive fentanyl delivery rate is 25 $\mu\text{g/hr}$. The electrically assisted portions of the device deliver ionic metoclopramide at a rate of about 25 mg metoclopramide per day.

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EXAMPLE III

A therapeutic system designed to transdermally deliver sufentanil base by passive delivery and sufentanil HCl by active delivery has a configuration similar to that illustrated in Figure 2. Sufentanil (both the base and salt forms) is a narcotic analgesic. The anodic donor electrode 22 and the cathodic counter electrode 23 have the same composition as described in Example I. Likewise, the ion-conducting adhesive layers 27 and 28, as well as the electrolyte reservoir 25 have the same composition as described in Example I. Separator 36 is composed of an ethylene vinyl acetate copolymer having a vinyl acetate content of 40% (EVA 40). EVA 40 is substantially impermeable to the passage of ionic species and therefore acts as an insulator between electrode assemblies 18 and 19.

Reservoir 34 contains both sufentanil base, which is in the form of neutral uncharged molecules and therefore is delivered passively, and sufentanil hydrochloride, which upon hydration of reservoir 34, dissolves to form sufentanil cations which are actively delivered. The reservoir 34 is prepared by adding 25 g low molecular weight PIB (average molecular weight of 35,000) and 25 g high molecular weight PIB (average molecular weight 1,200,000) to a stirring vessel. Light mineral oil (MO) is added to the same vessel with a ratio of approximately 1.125 to 1 part of PIB. Heptaene is added and the mixture is stirred until the polymers are dissolved. 25 wt% sufentanil base is added to the solution to generate a blend of sufentanil base in the PIB/MO.

Separately, 15 g of PVP-XL 10 and 10 g of sufentanil HCl are added to a stirring vessel. The mixture is stirred until the sufentanil salt was well blended in the PVP-XL 10. The PVP-sufentanil salt blend is then added to the PIB/MO sufentanil base blend and intimately mixed.

The device delivers sufentanil base passively from reservoir 34. In addition, when the power source is activated, the device delivers ionic sufentanil actively from reservoir 34. The passive sufentanil base delivery rate is 5 $\mu\text{g/hr}$. The electrically assisted ionic sufentanil delivery rate is 30 $\mu\text{g/hr}$ when the power source is turned on. This device is suitable for delivering a baseline level (e.g., 5 $\mu\text{g/hr}$) of sufentanil for the treatment of chronic pain, with the option of providing higher, patient activated delivery during episodes of severe pain.

Having thus generally described our invention and described in detail certain preferred embodiments thereof, it will be readily apparent that various modifications to the invention may be made by workers skilled in the art without departing from the scope of this invention and which is limited only by the following claims.

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CLAIMS

1. A transdermal agent delivery device, comprising:
an active agent reservoir adapted to be placed in
5 active agent transmitting relation with a body surface and positioned
within an electric field generated by electrically connecting the
active agent reservoir to a source of electrical power; and
a passive agent reservoir adapted to be placed in
passive agent transmitting relation to a body surface, the passive
10 agent being able to passively diffuse through the passive agent
reservoir, the passive agent reservoir being electrically insulated
from the electrical field generated by the power source.
2. The device of claim 1, including means for electrically
15 connecting and electrically disconnecting the power source and the
active agent reservoir.
3. The device of claim 1, wherein the passive agent
reservoir is ion permeable and the device includes an insulating
20 means which electrically insulates the ion permeable passive agent
reservoir from the electric field.
4. The device of claim 3, wherein the insulating means
comprises a hydrophobic polymer.
- 25 5. The device of claim 1, wherein the passive agent
reservoir is substantially ion impermeable.
6. The device of claim 5, wherein the passive agent
30 reservoir is positioned between (i) the active agent reservoir and
(ii) an electrolyte reservoir electrically connected to a counter
electrode.
7. The device of claim 5, wherein the passive agent
35 reservoir comprises a hydrophobic polymer matrix and the passive
agent.

8. The device of claim 4 or 7, wherein the hydrophobic polymer is selected from the group consisting of ethylene vinyl acetate copolymers, polyalkylenes, polyisoprenes, rubbers, polyvinyl acetate, polyamides, polyurethanes, polyvinyl chlorides, and modified
5 cellulosic polymers.

9. The device of claim 7, wherein the passive agent is soluble in the hydrophobic polymer matrix.

10. The device of claim 1, wherein the passive agent is
10 present in the passive agent reservoir in excess of saturation.

11. The device of claim 1, wherein the active agent is
ionizable.

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12. A transdermal agent delivery device, comprising:
an agent reservoir adapted to be placed in agent
transmitting relation with a body surface and positioned within an
electric field generated by electrically connecting the agent
20 reservoir to a source of electrical power, the agent reservoir
containing:

a nonionizable passively transported agent which
passively diffuses through the agent reservoir and through the body
surface; and

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an ionizable actively transported agent which is
actively delivered from the agent reservoir and through the body
surface.

13. The device of claim 12, including means for electrically
30 connecting and electrically disconnecting the power source and the
agent reservoir.

14. The device of claim 2 or 13, wherein the means for
electrically connecting and electrically disconnecting comprises an
35 on-off switch.

15. The device of claim 1 or 12, wherein the active agent comprises a water soluble salt.

16. The device of claim 1 or 12, wherein the active agent
5 comprises an ionizable salt of the passive agent.

17. The device of claim 1 or 12, wherein the passive agent is an acid or a base and the active agent is an ionizable salt of the acid or base.

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18. The device of claim 1 or 12, wherein the active agent and the passive agent are narcotic analgesics.

19. The device of claim 1, wherein the active agent reservoir
15 is comprised at least in part of a hydrophilic polymer matrix containing the active agent.

20. The device of claim 19, wherein the hydrophilic polymer is selected from the group consisting of polyvinyl pyrrolidones, polyvinyl alcohols, polyethylene oxides, acrylic polymers and cellulosic polymers.

21. A method of delivering an agent transdermally comprising:
a) placing a reservoir containing an actively
25 transported agent in agent transmitting relation with a body surface;
b) placing a reservoir containing a nonionizable passively transported agent in agent transmitting relation with a body surface to passively transport said agent through the body surface; and
30 c) generating an electric field through the reservoir containing the actively transported agent to actively transport said agent through the body surface.

22. The method of claim 21, including periodically
35 deactivating the electric field to stop the active transport of the active agent.

23. The method of claim 21, wherein the active agent is ionizable.

24. The method of claim 21, wherein the active agent
5 comprises a water soluble salt.

25. The method of claim 21, wherein the active agent comprises an ionizable salt of the passive agent.

10 26. The method of claim 21, wherein the passive agent is an acid or a base and the active agent is an ionizable salt of the acid or base.

27. A method of treating pain, comprising:
15 a) placing a reservoir containing an ionizable narcotic analgesic in narcotic analgesic transmitting relation with a body surface;
b) placing a reservoir containing a nonionizable narcotic analgesic in narcotic analgesic transmitting relation with a
20 body surface to passively transport said narcotic analgesic through the body surface;
c) dissolving the ionizable analgesic in a solvent to form narcotic analgesic ions; and
d) generating an electric field through the reservoir
25 containing the narcotic analgesic ions to actively transport said narcotic analgesic ions through the body surface.

28. The method of claim 27, wherein the ionizable narcotic analgesic and the nonionizable narcotic analgesic are contained in
30 the same reservoir.

29. The method of claim 27, wherein the ionizable narcotic analgesic and the nonionizable narcotic analgesic are contained in separate reservoirs, the reservoir containing the non-ionizable
35 narcotic analgesic being electrically insulated from the electric field.

30. The method of claim 27, wherein the ionizable narcotic analgesic comprises a salt of fentanyl or sufentanil.

31. The method of claim 27, wherein the nonionizable narcotic
5 analgesic comprises fentanyl base or sufentanil base.

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FIG. 1

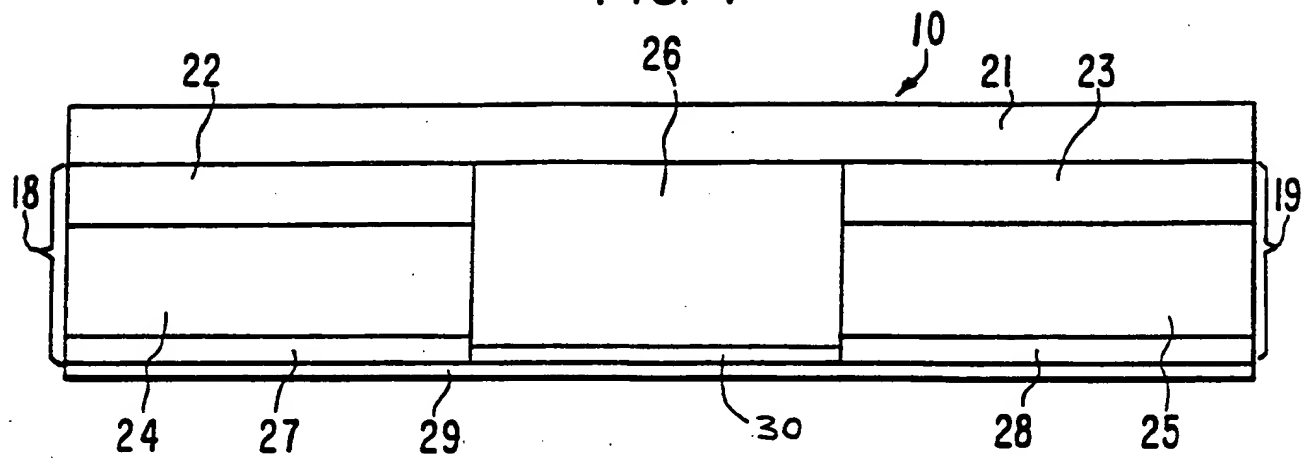
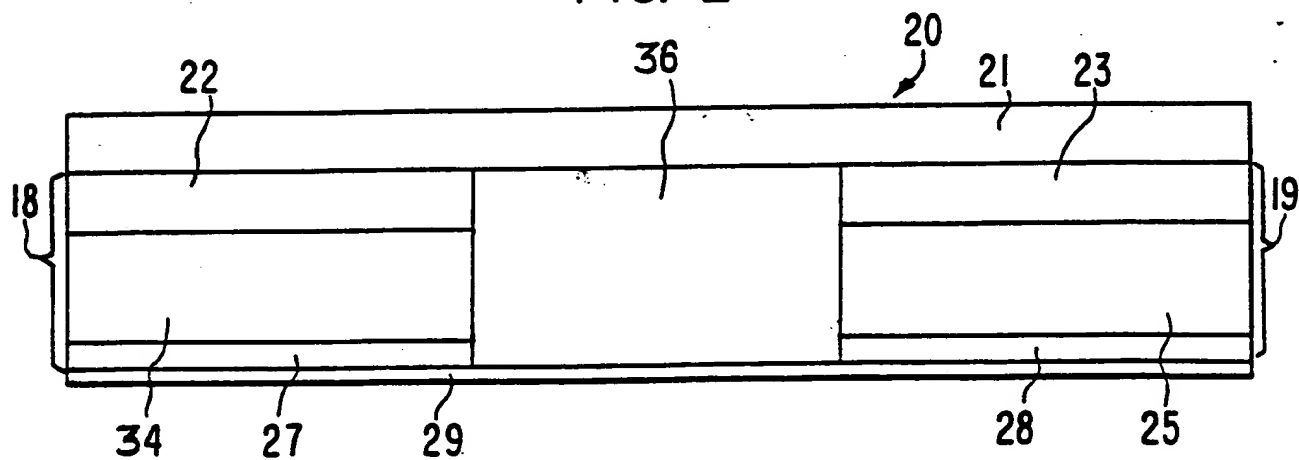


FIG. 2



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I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 A61K9/70; A61K9/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	US,A,4 640 689 (DAN SIBALIS) 3 February 1987 see the whole document -----	1-20
<p>¹⁰ Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 01 DECEMBER 1992		Date of Mailing of this International Search Report 07. 12. 92
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer VENTURA AMAT A.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/06151

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
ALTHOUGH CLAIMS 21-31 ARE DIRECTED TO A METHOD OF TREATMENT OF THE HUMAN BODY, THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOSITION.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9206151
SA 63281

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 01/12/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4640689	03-02-87	US-A- 4557723	10-12-85
		AU-B- 563137	25-06-87
		AU-A- 3185084	21-02-85
		CA-A- 1224993	04-08-87
		EP-A, B 0147524	10-07-85
		JP-A- 60060860	08-04-85
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		US-A- 4883457	28-11-89
		US-A- 4919648	24-04-90
		US-A- 4921475	01-05-90
		US-A- 5087240	11-02-92
		US-A- 4622031	11-11-86
		US-A- 5135479	04-08-92
		US-A- 4708716	24-11-87

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